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Autoimmunity through Cytokine-Induced Dendritic Cell Activation

Review

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We propose a model where autoimmunity can be viewed as a dynamic system driven by opposite vectors IFN-α/β and TNF. These cytokines drive differentiation of distinct types of DCs, TNF-DCs, or IFN-DCs, which present different antigens leading to distinct autoimmune responses. When balanced, both cytokines synergize in protective immunity. When one of the cytokines prevails, autoimmunity occurs, Type I interferons (IFN-α/β) playing a major role in systemic lupus erythematosus (SLE) and TNF playing a major role in rheumatoid arthritis. This model complements the Type 1/Type 2 paradigm. Therefore, immunity can be viewed as a dynamic system driven by two sets of opposite vectors: IFN-α/β/TNF and IFN-γ/IL-4.

Historical Perspective

The immune system evolved to protect us from microbes. The antigen (Ag)-nonspecific innate immunity and Ag-specific adaptive immunity (Fearon and Locksley, 1996; Medzhitov and Janeway, 1997) synergize to eradicate the invading pathogen through cells, such as dendritic cells (DCs) and lymphocytes, and through their effector proteins, including antimicrobial peptides, complement, and antibodies (reviewed in Palucka and Banchereau, 2002). Its intrinsic complexity renders the system prone to dysfunction, including cancer, autoimmunity, chronic inflammation, and allergy.

Immune cells use cytokines to communicate with each other. Cytokines, most particularly TNF (Feldmann and Maini, 2001) and Type I interferon, are regarded as essential factors in the development of autoimmunity. Identification of TNF as a major factor in the pathogenesis of rheumatoid arthritis and the development of anti-TNF therapy represent a success of immunology. Recognition of this success is demonstrated by the year 2003 Lasker Award being given to Drs. Feldman and Maini, pioneers of this field. Yet, it took more than two decades to understand the liaison between systemic lupus erythematosus (SLE) and Type I interferon (IFN-αβ). In 1979, Notkins et al. reported the presence of interferon activity in the serum of patients suffering from autoimmune diseases, including SLE, arthritis, and scleroderma (Hooks et al., 1979). The findings were subsequently confirmed mainly in SLE (Preble et al., 1982; von Wussow et al., 1988). The nature of circulating IFN has however represented a puzzle, as it was found to react with antibodies to Type I IFN yet it was acid labile, a property usually ascribed to IFN-γ (Preble et al., 1982). Further confirmation of the role of IFN-αβ in SLE came from the studies demonstrating induction of autoimmunity during IFN-αβ therapy (Ronnblom et al., 1991) and existence of circulating inducers of IFN-αβ in SLE patients' blood (Vallin et al., 1999).

Independent observations by several groups in the late 90s to early 00s led us to propose that SLE might indeed be due to a break in peripheral tolerance due to activation of myeloid dendritic cells (DCs) in response to an excess of IFN-αβ (Blanco et al., 2001). These milestones included the demonstration of (1) the critical role of immature DCs in the maintenance of peripheral tolerance (Steinman et al., 2003) that contrast with the ability of mature DCs to induce antigen-specific immunity (reviewed in Banchereau and Steinman, 1998; Banchereau et al., 2000; Lanzavecchia and Sallusto, 2001), (2) the remarkable capacity of plasmacytoid DCs (pDCs) to secrete large amounts of IFN-αβ upon exposure to viruses (Cella et al., 1999; Siegal et al., 1999) as well as bacterial DNA (Bauer et al., 2001; Krug et al., 2001), and (3) the ability of IFN-αβ to activate immature myeloid DCs (Luft et al., 1998; Paquette et al., 1998; Santini et al., 2000; Blanco et al., 2001).

Dendritic Cells

T and B cells are under the control of DCs (Steinman 1991; Banchereau and Steinman, 1998; Banchereau et al., 2000; Shortman and Liu, 2002), which thereby control immunity and tolerance (reviewed in Turley, 2002; Moser, 2003; Steinman et al., 2003). The first 25 years of DC research mostly focused on how they turn on immunity, particularly following microbial encounter. Immature, antigen-capturing mDCs sitting in peripheral tissues sense pathogens, tissue necrosis, and local inflammation. These signals induce DCs to undergo a maturation process while migrating through the afferent lymphatics into the T cell areas of draining lymph nodes. There, they present processed Ags to T cells via both classical (MHC class I and class II) and nonclassical (CD1 family) antigen-presenting molecules (Banchereau et al., 2000). This results in T cell proliferation and differentiation into helper and effector cells with unique function and cytokine profiles. DCs also activate B cells, NK cells, and NK T cells. Mature, antigen-loaded DCs are geared toward the launching of antigen-specific immunity (Finkelman et al., 1996) though recent data indicate that mature DCs also activate regulatory T cells. Immature (nonactivated) DCs capture and present self-antigens (e.g., apoptotic cells) to T cells (Albert et al., 1998a; Albert et al., 1998b; Heath and Carbone, 2001), which in the absence of appropriate costimulation leads to tolerance. How this complex balance is maintained in health and broken in autoimmunity is now starting to be understood.

In early 90s, culture systems were discovered that produced large amounts of mouse (Inaba et al., 1992) and human DCs, thereby accelerating their characterization (Caux et al., 1992; Romani et al., 1994; Sallusto and Lanzavecchia, 1994). Two major DC pathways are thought to exist (reviewed in Banchereau et al., 2000;

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Shortman and Liu, 2002): (1) a myeloid pathway, which generates at least two subsets, including Langerhans cells (LCs), found in stratified epithelia such as skin; and interstitial DCs (intDCs), found in all other tissues. These subsets display common and unique functions. Thus, while both subsets can produce IL-12 and induce naive $CD4^+$ T cell proliferation, only interstitial DCs produce IL-10 and can induce the differentiation of naive B cells into immunoglobulin-secreting plasma cells (Caux et al., 1996, 1997). Another pathway (2) includes plasmacytoid DCs (pDCs), which secrete, upon viral encounter, within a few hours large amounts of Type I interferon (Cella et al., 1999; Siegal et al., 1999). Therefore, pDCs represent a first barrier to the expansion of intruding viruses, thus acting as member of the innate immunity. Importantly, these cells subsequently differentiate into DCs able to induce immune responses, thus acting as members of adaptive immunity (Kadowaki et al., 2000). Thus, different DC subsets control different effector pathways of the immune system.

Dendritic Cells and Tolerance

Central Tolerance

The thymus steadily produces thymocytes expressing newly assembled TCR, some of which may be reactive with components of self. High-affinity autoreactive thymocytes are eliminated upon encountering self-MHC peptide (Marrack and Kappler, 1997; Sprent and Kishimoto, 2002; Starr et al., 2003). There is evidence that both thymic epithelial cells as well as mature DCs in the thymus may be involved in this process (Brocker, 1999; Fujimoto et al., 2002). The high frequency of circulating autoreactive T cells in the nonautoimmune repertoire indicates that central tolerance mechanisms are not sufficient to purge newly made T cells from their autoreactive elements. Therefore, autoreactive T cells that are not deleted in the thymus need to be controlled in the periphery to prevent immune responses to self. This is collectively described as peripheral tolerance.

Peripheral Tolerance through DCs

There is now evidence that immature DCs play an important role in peripheral tolerance (Steinman et al., 2003). Immature DCs within peripheral tissues capture cells dying by apoptosis and migrate through the lymphatics to the draining lymph node. These cells actually constitute the long recognized afferent flux of veiled cells (Pugh and MacPherson, 1982). Indeed, DCs loaded with apoptotic material are found in the steady-state within lymph nodes, draining tissues, such as the intestinal epithelium (Huang et al., 2000), the airway (Vermaelen et al., 2001), and the skin. Once they reach draining lymph nodes, immature DCs present self-peptide-MHC complexes, in the absence of costimulation signals, to the circulating naive autoreactive T cells. This results in their inactivation either by anergy or deletion. Immature DCs may also control peripheral tolerance through induction and maintenance of regulatory T cells (Cobbold and Waldmann, 1998; Roncarolo et al., 2001; Sakaguchi et al., 2001; Shevach et al., 2001; Bluestone and Abbas, 2003). The groups of M. Nussenzweig and R. Steinman have elegantly shown that fusion proteins targeted to DCs lead to antigen-specific tolerance induction when DCs are left immature (Bonifaz et al., 2002). Under these conditions, tolerance can be induced to an ongoing autoimmune disease, such as EAE, a model system for multiple sclerosis (M. Nussenzweig, personal communication). In contrast, a concomitant activation with anti-CD40 results in the mounting of a potent immune response, as DCs are induced to express a large number of costimulatory molecules (Bonifaz et al., 2004).

In vivo induction of tolerance to apoptotic cell components include a burst of T cell proliferation followed by their subsequent deletion. The capture and processing of cell-associated antigens in the periphery has been documented with the proton pump ATPase of the gastric parietal cells (Scheinecker et al., 2002). During autoimmune gastritis induced by thymectomy, the number of antigen-containing DCs increase in the draining node as well as the antigen-presenting function of these DCs (Scheinecker et al., 2002). Selective deletion of DCs using specific toxins (Jung et al., 2002) was found to avoid the depletion of antigen-specific T cells by antigen-loaded dying splenocytes. Such tolerance mechanisms permit to prevent or reduce the development of autoimmunity when dying cells are generated and processed at the time of infection (Liu et al., 2002).

It can thus be easily imagined that "inappropriate" activation of what should otherwise be an immature, tolerogenic DC may lead to the break of peripheral tolerance and launch immunity to self-antigens.

Unique Alterations in Systemic Lupus Erythematosus Blood

Systemic lupus erythematosus (SLE) is a prototype autoimmune disease characterized by a break of tolerance to nuclear components and profound alterations of the immune system (Desai-Mehta et al., 1996; Marrack et al., 2001; Shlomchik et al., 2001; Wakeland et al., 2001).

SLE Patients Display Considerable Lymphopenia

SLE patients display considerable lymphopenia that affects both T cell and B cell compartments. The B cell compartment presents several unusual features (Odendahl et al., 2000; Arce et al., 2001; Lipsky 2001). There is a major decrease in the frequency and numbers of both naive and memory B cells. In contrast, pregerminal center cells that express CD38 are found in increased frequency but not increased numbers (Arce et al., 2001). Plasmablasts, however, represent a significant fraction of the B cell pool, as their numbers are increased 3-fold when compared to healthy age-matched individuals (Odendahl et al., 2000; Arce et al., 2001). T cells are also decreased in numbers and appear to react differently from normal cells, as they are more resistant to activation (Tsokos et al., 2003). Importantly, SLE $CD8^+$ T cells appear to express higher levels of granzymes, and their number correlates with disease severity (P. Blanco, personal communication). Overexpression of effector molecules involved in cell lysis may not be restricted to $CD8^+$ T cells, as $CD4^+$ T cells from patients with active SLE show perforin overexpression as well (Kaplan et al., 2004). Such enhanced activity of cytotoxic lymphocytes could be targeted against autologous cells (for example, monocytes; Kaplan et al., 2004) and may contribute the source of autoantigens (Casciola-Rosen et al., 1994, 1999).

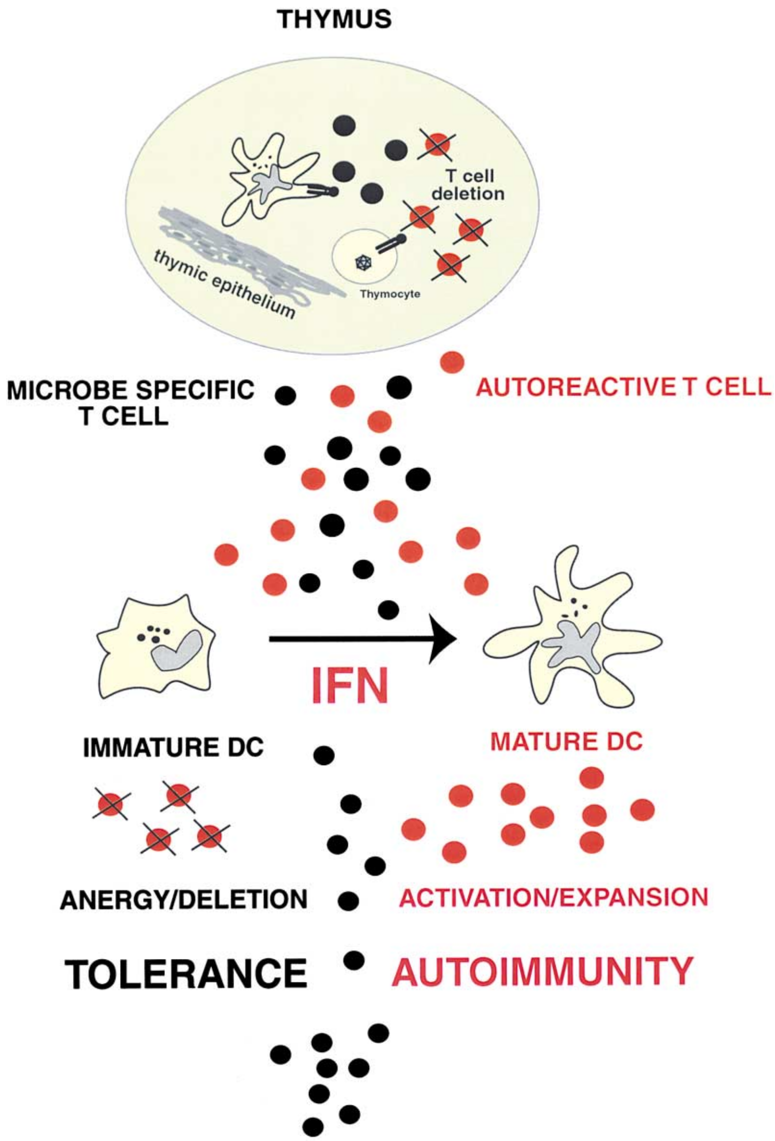

Figure 1. Fate of Autoreactive T Cells

Autoreactive thymic escapees are silenced in periphery via immature DCs, which control peripheral tolerance. Excess IFN-$\alpha\beta$ induces unabated DC maturation, which leads to activation/expansion of autoreactive T cells.

DCs Numbers Are Reduced in SLE Blood

Myeloid DCs (mDCs), characterized as CD14$^-$CD11^{hi} HLA-DR$^+$ cells, are reduced by about 30% in the blood of SLE patients, which is barely significant. Plasmacytoid DCs (pDCs), characterized as CD123^{hi}, HLA-DR^{lo}, and Lin^{neg}, are reduced by as much as 70% (Blanco et al., 2001; Gill et al., 2002). This is consistent with the early description of reduced numbers of IFN-$\alpha\beta$-producing cells in SLE blood in response to DNA-anti-DNA immune complexes (Cederblad et al., 1998). This reduction in numbers is not solely due to the effect of medication, as the blood was analyzed at the time of diagnosis, before treatment initiation. This is an important consideration, as steroids, a classic treatment of SLE, can reduce the number of pDCs to nearly zero when administered at high dose (Shodell et al., 2003).

SLE Monocytes Act as DCs

CD14$^+$ blood cells are normally immunologically quiescent monocytes that are unable to mount the so-called mixed lymphocyte reaction (MLR). However, in SLE these cells are able to induce the proliferation of alloreactive T cells, a property characteristic of DCs (Blanco et al., 2001). It is generally accepted that DCs do not express CD14 because the blood CD11c$^+$ mDCs and the DCs generated in vitro with a combination of GM-CSF and IL-4 do not express CD14. Yet, DCs made by culturing monocytes with a combination of GM-CSF and IFN (Santini et al., 2000) or GM-CSF and IL-15 (Mohamadzadeh et al., 2001) do express CD14. Indeed, incubation of monocytes from healthy individuals with serum from active SLE patients results in the generation of CD14$^+$ cells with certain characteristics of DCs, including phenotype and ability to induce an MLR. Neutralizing anti-IFN-$\alpha\beta$ have demonstrated IFN-$\alpha\beta$ to be the key SLE serum factor responsible for the differentiation of monocytes into DCs. Furthermore, normal serum spiked with recombinant IFN-$\alpha\beta$ can also induce the differentiation of monocytes into DCs. SLE serum contains other cytokines that may participate in the DC-induction effect. In particular, high levels of CD40 ligand are found

(Desai-Mehta et al., 1996; Kato et al., 1999; Vakkalanka et al., 1999) and increased levels of FLT-3L correlate with disease severity (Gill et al., 2002). These IFN-driven DCs capture apoptotic cells and present their antigens to T cells (Blanco et al., 2001). Indeed, SLE may be viewed as a problem in the processing of apoptotic cells by DCs (Bellone et al., 1997) rather than by macrophages (Fadok et al., 1992; Baumann et al., 2002).

IFN-α Signature in SLE

The quantitation of IFN in SLE serum can be performed by ELISA or using antiviral bioassays. In all cases, only a fraction of the patients display detectable circulating IFN-αβ. Yet, microarray analysis of blood mononuclear cells demonstrates that the vast majority of patients we have analyzed to date (68/70 children and 11/11 adults) display an IFN signature (Baechler et al., 2003; Bennett et al., 2003). In addition to the IFN-αβ signature, another unique signature, that of immature granulocytes, could be found in most of the patients suffering from the most severe form of the disease (Bennett et al., 2003). Interestingly, an antimicrobial peptide (defensin DEFA-3) was among the genes that correlate best with disease activity. As defensins have been shown to activate DCs (Biragyn et al., 2002), their overexpression may add to the overall DC activation in SLE. The typical SLE PBMCs signature cannot be found in other autoimmune diseases tested to date, including the various kinds of juvenile idiopathic arthritis. Importantly, the SLE signature differs from that found in patients acutely suffering from viral infections like influenza virus or herpes virus (our unpublished data) though an IFN-αβ signature can also be found in these patients' PBMCs.

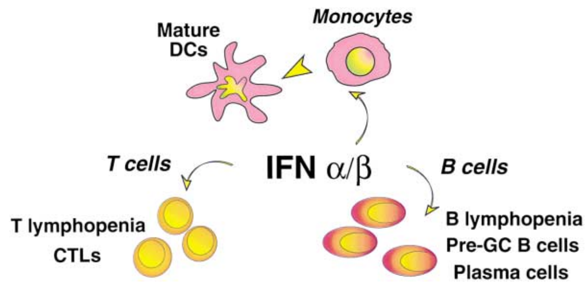

Figure 2. IFN-α as a Pathogenic Factor in SLE

High levels of IFN-α in SLE might explain several immunological findings of this disease, including (1) permanent maturation of myeloid DCs resulting in activation rather then silencing of autoreactive T cells and autoantigen presentation from captured apoptotic cells; (2) T lymphopenia (Lin et al., 1998), concomitant with expansion of effector T cells overexpressing granzymes and perforin; and (3) B lymphopenia (Lin et al., 1998), concomitant with the expansion of $CD38^{+}$ GC-like B cells (Galibert et al., 1996) found in SLE blood and accelerated plasma cell differentiation.

pDCs Drive Plasma Cell Differentiation through IFN-α

SLE has long been thought of as an alteration of the B cell compartment with increased generation of plasma cells and production of autoantibodies (Shlomchik et al., 2001). Given the central role of IFN-αβ in SLE, the question arises as to whether IFN-αβ might be responsible for the increased frequency of plasma cells in this disease (Jego et al., 2003). Indeed, activated B cells exposed to IFN-αβ differentiate into CD38hi CD20neg plasmablasts that do not secrete much immunoglobulins (Jego et al., 2003). However, upon exposure to IL-6, another pDC product, the IFN-αβ-generated plasmablasts, differentiates into highly efficient Ig-secreting plasma cells. Activated B cells exposed to virus-triggered pDCs differentiate into efficient Ig-secreting plasma cells in both IFN-αβ- and IL-6-dependent manner. Strikingly, the plasma cells generated under these conditions express very high levels of CD38, similar to that of plasma cells isolated from lymphoid tissues. In contrast, plasma cells generated by culturing activated B cells with the T cell-derived cytokines IL-2 and IL-10, though efficient Ig secretors, do not express high levels of CD38 (Arpin et al., 1995). This suggests that IFN-αβ may represent an important cytokine in the generation of tissular plasma cells. Indeed, studies in the mouse have also found that IFN-αβ is an excellent adjuvant for humoral immunity (Le Bon et al., 2001). However, there may also be an indirect contribution of IFN-α to plasma cell differentiation because activated myeloid DCs can induce B cell growth and differentiation (Dubois et al., 1997, 1998; Fayette et al., 1997; Litinskiy et al., 2002). Several molecules have been shown to be involved in this process, including IL-12, IL-6 (Banchereau et al., 2000), and, more recently, BAFF/Blys (Schneider et al., 1999; Batten et al., 2000; Gross et al., 2000; Balazs et al., 2002; MacLennan and Vinuesa, 2002), a molecule upregulated by IFN-α, which overexpression of in mice induces lupus-like syndrome (Mackay et al., 1999). Furthermore, immature neutrophils might represent a considerable source of Blys (Scapini et al., 2003) thus contributing to altered B cell homeostasis in SLE.

Systemic Lupus Erythematosus as an IFN-α-Driven Disease

SLE is a remitting disease characterized by flares that progressively result in deterioration of the patient. These flares are often associated to viral infections. The infection in SLE, which might represent a primary element in disease development, triggers unabated production of IFN-αβ. This increased bioavailability of IFN-αβ induces and maintains the generation of mature DCs. The increase of mature DCs and decrease of immature DCs therefore tilts the fate of autoreactive T lymphocytes from deletion to activation. Indeed, tissue turnover permanently generates apoptotic cells, which are captured by immature DCs. These cells present apoptotic cell-derived antigens, including nuclear antigens, to autoreactive T cells in a manner that results in their silencing/deletion. In contrast, mature DCs, which are induced in SLE by IFN-αβ, will activate and expand these T cells. Thus, a high-affinity autoreactive T cell that exits from the thymus will eventually be activated and expanded (Figure 1). This creates a first autoimmune injury, which might then be amplified by a vicious circle of self-antigen capture and presentation by IFN-DCs (Figure 2).

Several scenarios could be contemplated to explain the break of B cell tolerance and generation of anti-DNA antibodies. (1) IFN-DCs would present autoantigens to CD4 T cells and the expanded autoreactive T cells would help differentiation of autoantibody-producing B cells,

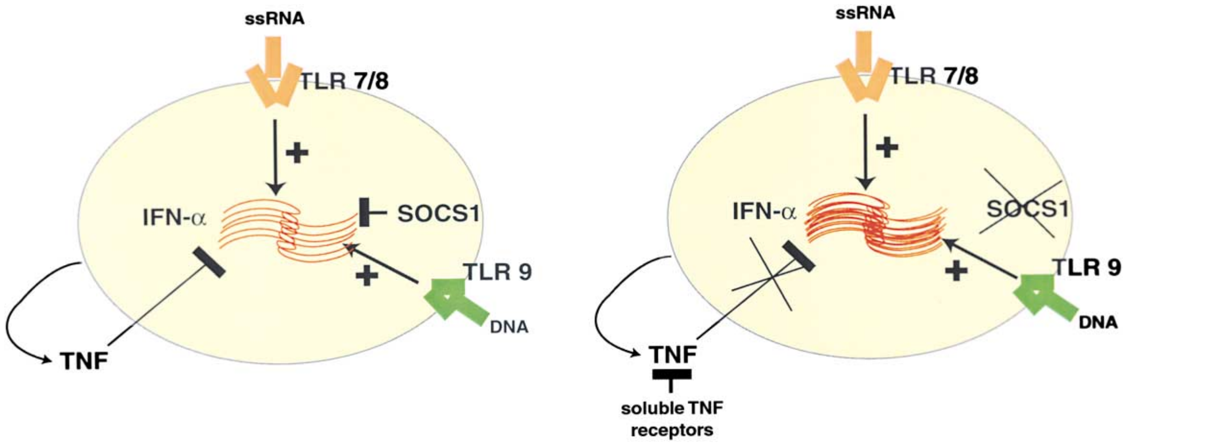

Figure 3. Mechanisms of Excess IFN-αβ

Virus triggers IFN-αβ secretion that normally is controlled by SOCS1 and/or by TNF. Continued presence of TLR7 or TLR9 ligands, for example, virus, or DNA-anti-DNA immune complexes, sustains IFN-αβ production, which is further supported by deletion of SOCS1 function (through genetic alteration) and/or by TNF blockade via soluble TNF receptors.

in a classical ménage a trois (Banchereau and Steinman, 1998). (2) B cells are activated in a T cell-independent fashion, through combined B cell receptor and TLRs engagement, for example, with chromatin-containing immune complexes (Leadbetter et al., 2002; Viglianti et al., 2003). Indeed, the majority (55%–75%) of all antibodies expressed by early immature B cells from healthy individuals display self-reactivity, including polyreactivity and antinuclear specificities (Wardemann et al., 2003). While these self-specificities are normally removed from the repertoire at discrete checkpoints during B cell development (Wardemann et al., 2003), IFN alone and/or IFN-DCs could alter these checkpoints and allow the differentiation of some of these autoreactive clones into fully secreting plasma cells. Indeed, there is evidence that DCs can present antigens directly to B cells (Wykes et al., 1998; Macpherson and Uhr, 2004) and induce their maturation and isotype switch (Dubois et al., 1997, 1998; Fayette et al., 1997; Litinskiy et al., 2002). The ensuing immune complexes would then amplify and perpetuate the above described B cell activation loop. This, however, may not explain the initiation of the disease before anti-DNA antibodies are made (Arbuckle et al., 2003). (3) SLE patients may display genetically imprinted alterations in the autoreactive B cell checkpoints that are independent from IFN and DCs and would allow the survival of autoreactive clones into the peripheral compartment. IFN and/or IFN-DC would just contribute to the activation and differentiation of these clones into autoantibody-secreting plasma cells. In favor of this last possibility, healthy relatives of SLE patients often display antinuclear antibodies. Similarly, B6.Sle1 congenic mice display intrinsic B cell alterations that lead to the development of anti-chromatin antibodies in the absence of T cell help. In spite of the high autoantibody titers, these mice do not develop further SLE manifestations (Sobel et al., 2002).

A critical point that remains to be clarified is the mechanism leading to unabated production of IFN-αβ in SLE (Figure 3). IFN-αβ can be produced by many cell types (Biron et al., 1999; Katze et al., 2002), many currently viewing the pDC as a main producer of IFN-αβ (Cella et al., 1999; Siegal et al., 1999; Kadowaki et al., 2000; Asselin-Paturel et al., 2001). Indeed, while pDCs are significantly decreased in the SLE blood (Blanco et al., 2001; Gill et al., 2002), they accumulate in the skin at the site of the typical SLE rashes (Blomberg et al., 2001; Farkas et al., 2001). This is where they might produce the IFN-αβ in excess, as the microarray analysis did not reveal increased transcription of IFN molecules in SLE blood (Bennett et al., 2003). Other cell types may however contribute to the excessive IFN-αβ production. For instance, IFN-αβ triggers TLR7 expression on monocytes and DCs, which can be induced to produce IFN-αβ in response to TLR7 agonists (Mohty et al., 2003), such as virus-derived single-stranded RNA (Diebold et al., 2004; Heil et al., 2004). Mechanisms that may lead to IFN-αβ oversecretion include: (1) genetic alterations that result in unabated secretion of IFN-αβ. The alteration may be within the IFN secretion mechanism, as exemplified by SLE in SOCS-1$^{-/-}$ mice (Hanada et al., 2003). (2) The increased levels of soluble TNF receptors in SLE serum, which may contribute to sustained IFN production by blocking TNF, which by itself shuts down the production of IFN, as discussed later. (3) The presence of immune complexes containing either RNA or DNA, which, through triggering of TLR-7 and 9, respectively, may sustain IFN production by pDCs (Bave et al., 2001). Indeed, the development of SLE is believed to require a combination of environmental, e.g., viruses, and genetic alterations. Our recent studies in mice demonstrate that sustained administration of low levels of IFN-α can dramatically precipitate the onset of the disease in NZB/W F1 while leaving normal mice unaffected (A. Mathian, S. Koutouzov, and J.B., unpublished data). Furthermore, crossing both NZB and B6 lpr/lpr mice with a Type I IFN receptor KO strain significantly decreases morbidity and prolongs mouse survival (Braun et al., 2003; Kono et al., 2003; Santiago-Raber et al., 2003). Taken together, these data also demonstrate the importance of IFN-αβ in mouse models of SLE.

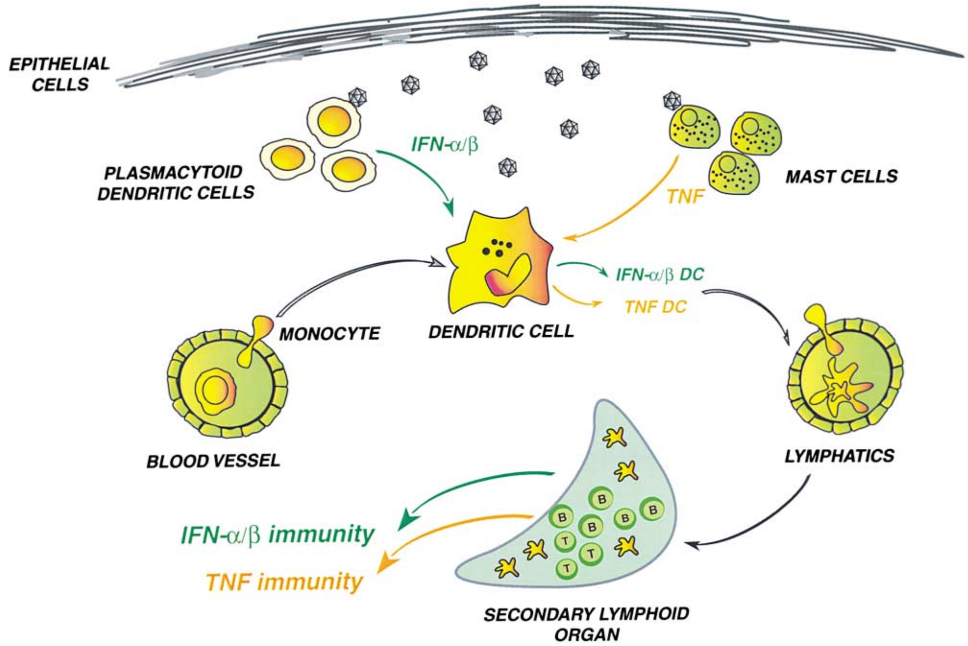

Figure 4. The Weight of Cytokine Environment on DC Differentiation/Maturation

Microbes can induce DC maturation directly via pattern recognition receptors on DCs. Alternatively, other cell types, including stromal cells (epithelial cells, keratinocytes, and fibroblasts), mast cells, plasmacytoid DCs, and NK cells respond to microbes by secreting different cytokines (IFN-α/β, TNF, IFN-γ, IL-4, IL-15, IL-1, etc.). Such cytokines activated DC differentially yielding distinct subsets that induce distinct types of immune responses.

Crossregulation of TNF and IFN-α in Autoimmune Diseases

It is now well accepted that TNF plays a critical role in pathogenesis of autoimmune diseases, such as rheumatoid arthritis (Feldmann and Maini, 2001) and psoriasis (Gottlieb, 2003). Accordingly, TNF antagonists have proven to be efficient therapy of RA (Feldmann and Maini, 2001) and psoriasis (Leonardi et al., 2003). However, these antagonists may lead to clinical complications, such as reactivation of tuberculosis (Gomez-Reino et al., 2003) and reversible SLE (reviewed in Reimold, 2002; Ehlers, 2003). Conversely, anti-TNF therapy is not effective in patients with SLE and may in fact worsen clinical symptoms of this disease. These clinical observations suggest that TNF might regulate IFN-α production. Indeed, TNF inhibts IFN-α release by pDCs exposed to influenza virus and completely blocks pDCs generation from CD34$^+$ hematopoietic progenitors (our unpublished data). Conversely, TNF antagonists enhance the production of IFN-α/β by pDCs exposed in vitro to viruses. Furthermore, treatment of patients suffering from systemic onset juvenile idiopathic arthritis with anti-TNF induces overexpression of IFN-α-regulated genes in blood leukocytes (our unpublished data). These results may thus provide a mechanistic explanation for the increased anti-dsDNA antibodies and lupus-like syndrome in a fraction of patients treated with TNF antagonists. Conversely, high levels of soluble TNF receptors in SLE (Gattorno et al., 1998; Davas et al., 1999; Gill et al., 2002) may block endogenous TNF. The TNF-mediated downregulation of the Type I interferon pathway could also explain earlier observations in the mouse lupus model NZB/W, which bear a genetic deficiency of TNF (Jacob et al., 1990). Consequently, these mice benefit from replacement therapy with recombinant TNF (Jacob and McDevitt, 1988).

On the other side of the spectrum, there is evidence that IFN-α/β may regulate TNF. For example, TNF is implicated in the pathogenesis of multiple sclerosis (Hofman et al., 1989; Selmaj et al., 1991) and is involved in EAE, an experimental model for multiple sclerosis. IFN-β knockout mice seem more susceptible to EAE than the wild-type (Teige et al., 2003), and administration of IFN-β to mice with EAE inhibits disease progression (Yu et al., 1996). In humans, IFN-β can inhibit in vitro TNF production by microglia, either directly or by attenuating the ability of T cells to trigger TNF secretion by microglial cells (Chabot et al., 1997). This regulatory mechanism might partially explain the beneficial effect of IFN-β therapy in this disease (Chabot et al., 1997). Furthermore, PBMCs from healthy volunteers injected with IFN-β show markedly decreased secretion of TNF and lymphotoxin as compared to placebo-treated volunteers (Rothuizen et al., 1999).

Taken together, our data open a new way to look at the control of autoreactive immune responses, which have been challenging to integrate within the Th1/Th2 paradigm (Mosmann and Coffman, 1989; Romagnani, 1995). We therefore propose to extend this paradigm and integrate two antagonistic paths, i.e., the IFN path and the TNF path. These paths lead to contrasting immune responses, which might yield opposite pathologies, i.e., lupus and arthritis (Figure 4).

Different Cytokines Generate Different DCs that May Lead to Different Autoimmune Syndromes

In response to microbial infection, cells from the invaded tissue secrete different cytokines. The cytokines may

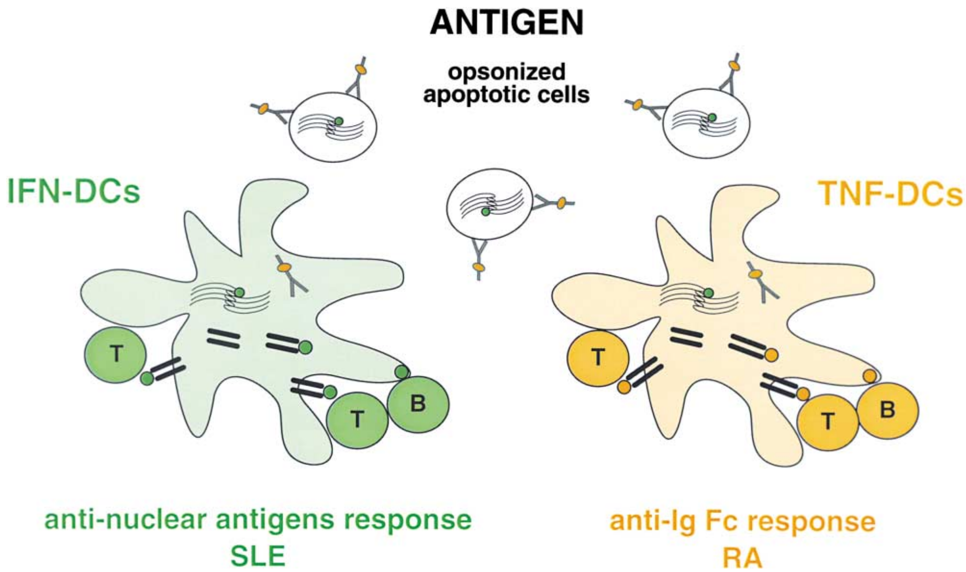

Figure 5. Distinct DC Subsets Induce Different Autoimmune Response, Leading to Different Autoimmune Diseases

IFN-α/β and TNF will generate distinct DC subsets. These DCs will capture opsonized apoptotic bodies. Distinct proteolytic enzymes expressed by these distinct DC subsets will generate distinct repertoire of peptides leading to a distinct set of MHC peptide complexes and, thus, a distinct antigen-specific lymphocyte repertoire. IFN-DCs will present nuclear antigens eventually leading to generation of anti-dsDNA antibodies typical of SLE. In contrast, TNF-DCs will present Fc fragment of immunoglobulins eventually leading to generation of rheumatoid factor typical of rheumatoid arthritis.

differ for several reasons: (1) they may originate from different cells (e.g., keratinocytes, fibroblasts, or mast cells) (Benoist and Mathis, 2002) or (2) the same cell may secrete different cytokines in response to different microbial components. These cytokines will induce attracted monocytes to differentiate into either macrophages that can digest and destroy the microbes or DCs that will permit the launching of specific immune responses (Banchereau and Steinman, 1998; Randolph et al., 1999; Banchereau et al., 2000; Chomarat et al., 2000, 2003). The different cytokines that may be produced skew the differentiation of monocytes into different DCs. For example, when monocytes encounter IL-4, they will yield IL4-DCs (Peters et al., 1993; Romani et al., 1994; Sallusto and Lanzavecchia, 1994). Upon encounter with IFN-α or TNF, they will differentiate into IFN-DCs (Luft et al., 1998; Paquette et al., 1998; Santini et al., 2000; Blanco et al., 2001) or TNF-DCs (Chomarat et al., 2003), respectively (Figure 4). Each DC subset displays common as well as unique biological functions determined by a unique combination of cell surface molecules and cytokines. Indeed, while IL-4 DCs represent a homogenous population of cells devoid of Langerhans cells, TNF-DCs are heterogeneous and include both CD1a^{+} Langerhans cells and CD14^{+} interstitial DCs (Chomarat et al., 2003). The latter subsets differ in their

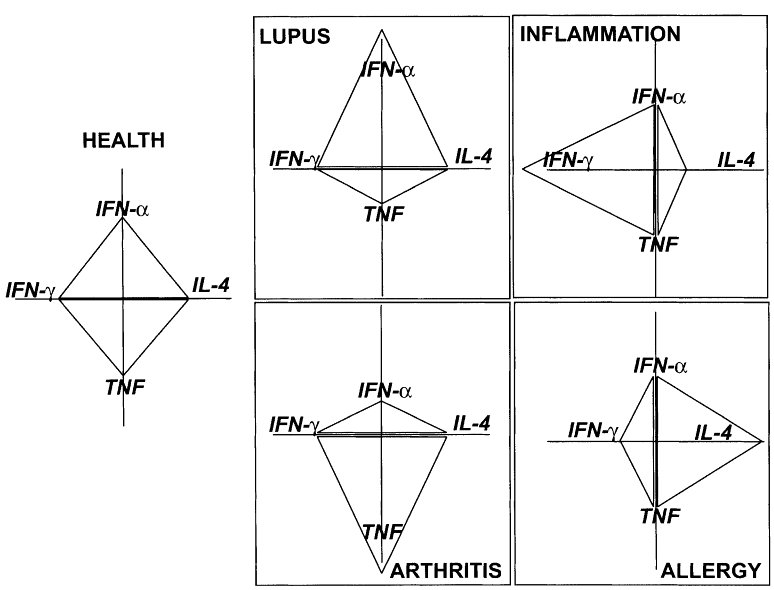

Figure 6. The Four Arms of Immune Homeostasis and Disease

Immunity is viewed as a dynamic system driven by two sets of opposite vectors, i.e., TNF and IFN-α/β, IL-4 and IFN-γ. The sum of the vectors yields an equilibrium point, which allows protective immunity when vectors are equal. This dynamic system can accommodate a prevalence of either vector. However, when one of the vectors prevails beyond a certain threshold, the equilibrium point moves into a zone of autoimmunity. Thus, when TNF vector prevails, then TNF-mediated autoimmunity will occur, such as arthritis. When IFN-α/β vector prevails, then IFN autoimmunity will occur, including SLE, thyroiditis, and diabetes. The prevalence of IL-4 will drive allergy while IFN-γ will sustain inflammation. The prevalence of one vector may be due to its absolute strengthening due to its increased production or its relative strengthening due to the weakening of the opposite vector.

capacity to activate naive B cells in the cytokines that they secrete as well as in their enzymatic activity (Caux et al., 1996, 1997). The latter property may be fundamental for the induction of immune responses, as different enzymes are likely to degrade a given antigen into a different peptide repertoire. For example, tripeptidyl peptidase II can generate proteasome-independent epitopes of HIV nef protein (Seifert et al., 2003). Thus, distinct DC subsets with distinct proteolytic enzymes will generate distinct repertoire of peptides leading to a distinct set of MHC peptide complexes and, thus, a distinct antigen-specific T cell repertoire. This concept can be illustrated by TNF- and IFN-α/β-driven differentiation of distinct types of DCs. Thus, IFN-DCs will present nuclear antigens, eventually leading to generation of anti-dsDNA antibodies typical of SLE. In contrast, TNF-DCs will present Fc fragment of immunoglobulins, eventually leading to generation of rheumatoid factor typical of rheumatoid arthritis (Figure 5). Furthermore, differentiated DCs also respond to their cytokine microenvironment, which ultimately shapes the type of T cell responses. For example, Th1-inducing DCs, when exposed to IL-10 and TGF-β, can induce Th2-like responses (Kalinski et al., 1999). Conversely, IFN-γ can instruct DCs to acquire some Th1-inducing capacity (Vieira et al., 2000). Therefore, these unique DCs will yield unique immune effectors that permit eradication of the invading microbes. The generation of a considerable number of distinct effectors will permit the successful handling of a large variety of potentially harmful microbes, but also, if out of control, a unique pathology.

We therefore propose a simple view of dendritic cells and ensuing immunity as a wind rose, which, rather than pointing toward North/South and East/West, is composed of TNF/IFN-$\alpha\beta$ and IL-4/IFN-γ (Figure 6). There, immunity is viewed as a dynamic system driven by two sets of opposite vectors, i.e., TNF and IFN-α/β, IL-4 and IFN-γ. The sum of the vectors yields an equilibrium point, which allows protective immunity when vectors are equal. This dynamic system can accommodate the prevalence of either vector to a certain extent. However, when one of the vectors prevails beyond a certain threshold, the equilibrium point moves into a zone of immunopathology, such as autoimmunity, allergy, or inflammation. Thus, when TNF vector prevails, then TNF-mediated autoimmunity will occur, such as arthritis. When IFN-α/β vector prevails, then IFN autoimmunity will occur, including SLE, thyroiditis, and diabetes. The prevalence of IL-4 will drive allergy while IFN-γ will sustain inflammation. The prevalence might be due to increased bioavailability of one cytokine or decreased bioavailability of the other one. As each cytokine will drive differentiation of a unique DC subset, understanding of dendritic cell heterogeneity is critical to a better understanding of the immune responses, most particularly as it applies to immunopathology and immunotherapy.

Undoubtedly, the years to come will be exciting, as the better understanding of the immune system will permit major therapeutic progresses in many areas of medicine.

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